



Demystifying Medicine Lecture

January 14, 2020



Ebola: Then, Now and the NIH Role

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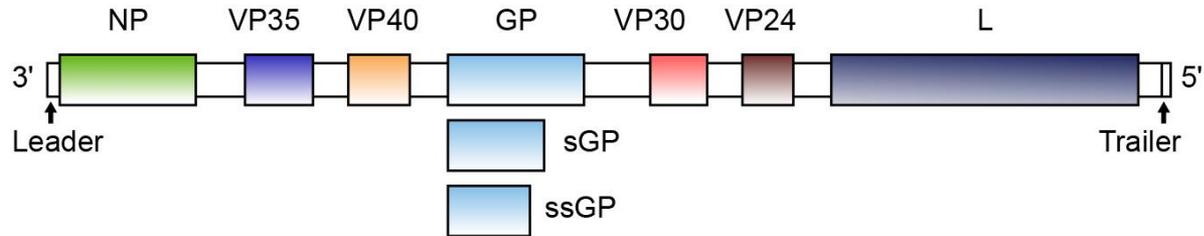
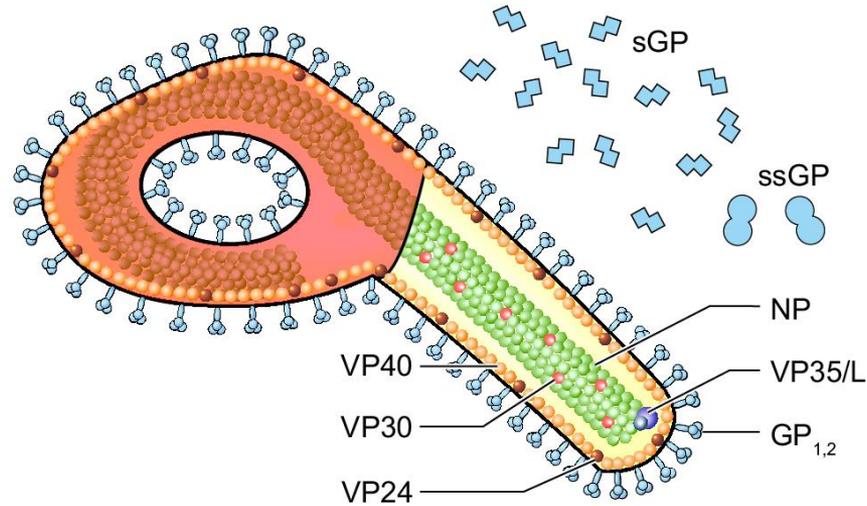
Disclosures

- Relevant Financial Disclosures
 - None
- Non-FDA Approved Use of Medications
 - None

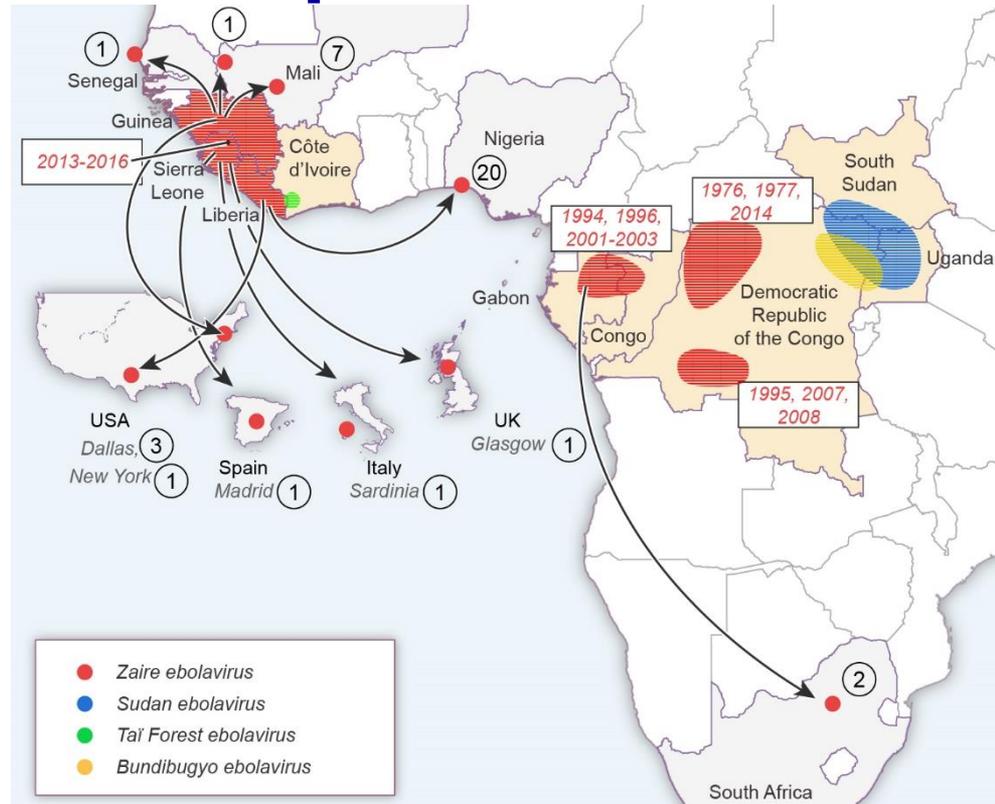
Lecture Objectives

- Overview of prior and current Ebola virus outbreaks
- NIH's role caring for a critically ill patient with Ebola virus disease
 - Clinical course and MRI findings
 - Molecular/immunologic correlates of disease

Ebolavirus

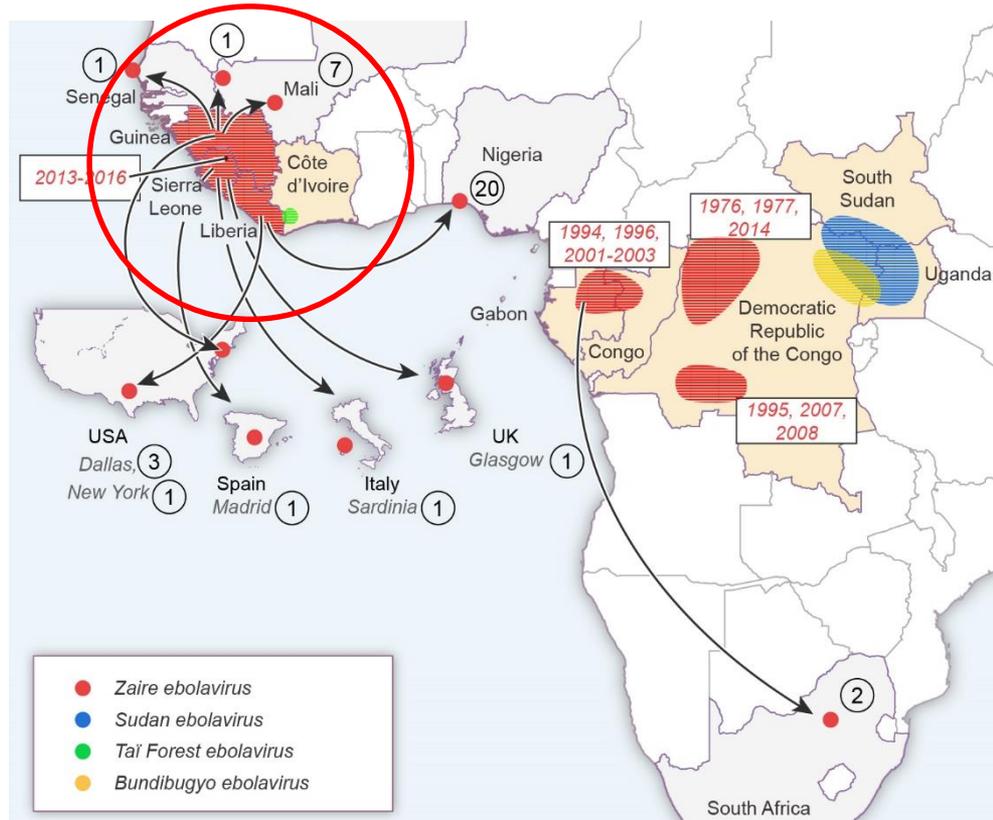


Location of outbreaks associated with 4 ebolavirus species from 1976-2013



2013-16 Ebola virus outbreak in West Africa

28,616 cases
11,310 deaths



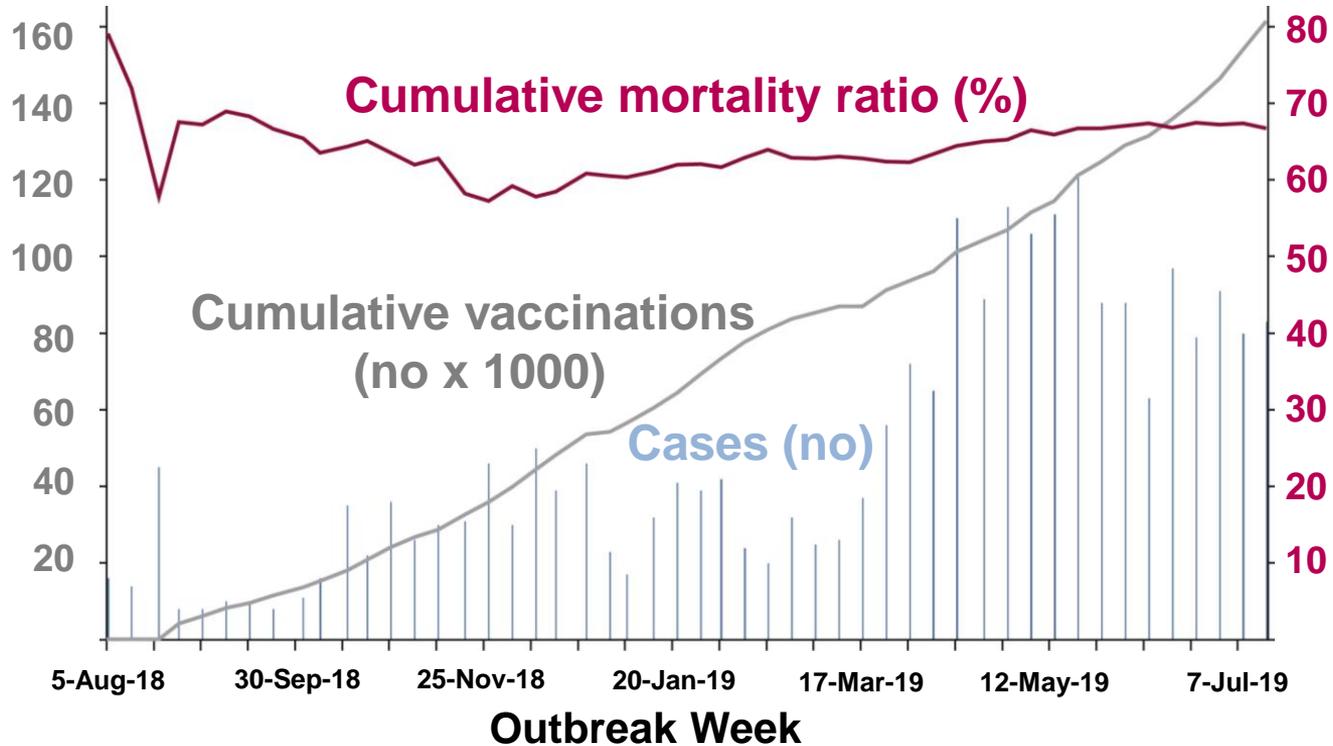
Improved care environment, DRC 2018

3395 cases
2,235 deaths



Photo courtesy of Dr. Ian Crozier

Despite promising vaccines and therapies overall mortality from EVD remains high



ELWA-3 Ebola treatment center, Monrovia Liberia, September 2014



Early clinical observations from the 2013-16 EVD outbreak in West Africa

Clinical Features of Ebola Virus Disease.

Phase of Illness	Time since Symptom Onset	Clinical Features
Early febrile	0–3 days	Fever, malaise, fatigue, body aches
Gastrointestinal	3–10 days	Primary: epigastric pain, nausea, vomiting, diarrhea Associated: persistent fever, asthenia, headache, conjunctival injection, chest pain, abdominal pain, arthralgias, myalgias, hiccups, delirium
Shock or recovery	7–12 days	Shock: diminished consciousness or coma, rapid thready pulse, oliguria, anuria, tachypnea Recovery: resolution of gastrointestinal symptoms, increased oral intake, increased energy
Late complications	≥10 days	Gastrointestinal hemorrhage, secondary infections, meningoencephalitis, persistent neurocognitive abnormalities*

Clinical course of Ebola virus disease survivor treated at NIH

Presenting illness of NIH patient

A 34 year old male healthcare worker volunteering in an Ebola treatment unit (ETU) in Sierra Leone developed onset of fatigue and malaise on March 7th, 2015

Confirmation of Ebola virus disease

His illness progressed with fever to 38.5°C, weakness, and muscle pain. On March 10th he was evaluated in a British ETU where he was confirmed to be Ebola virus + by RTqPCR testing of a blood sample.

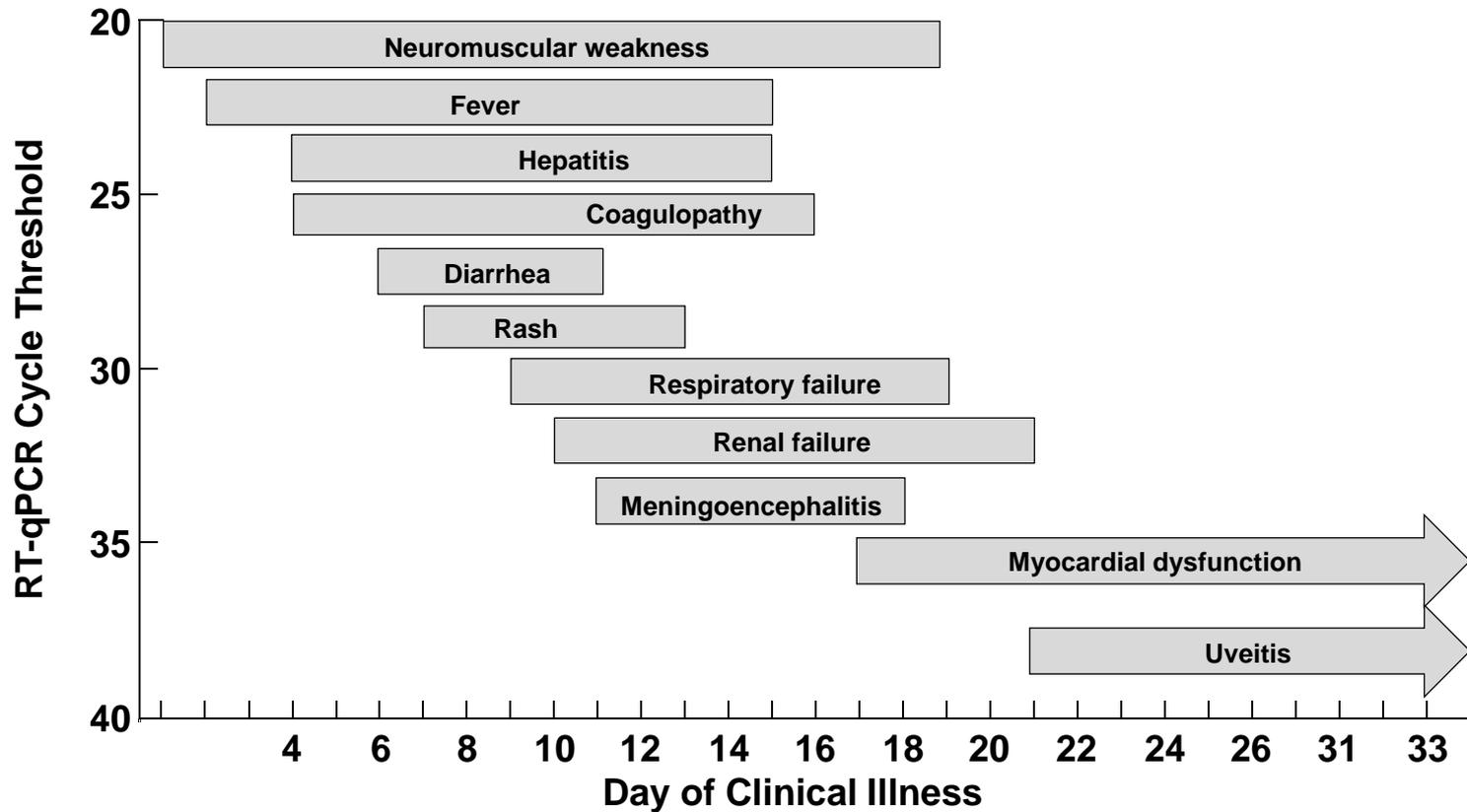
NIH patient arrives in US— March 13, 2015



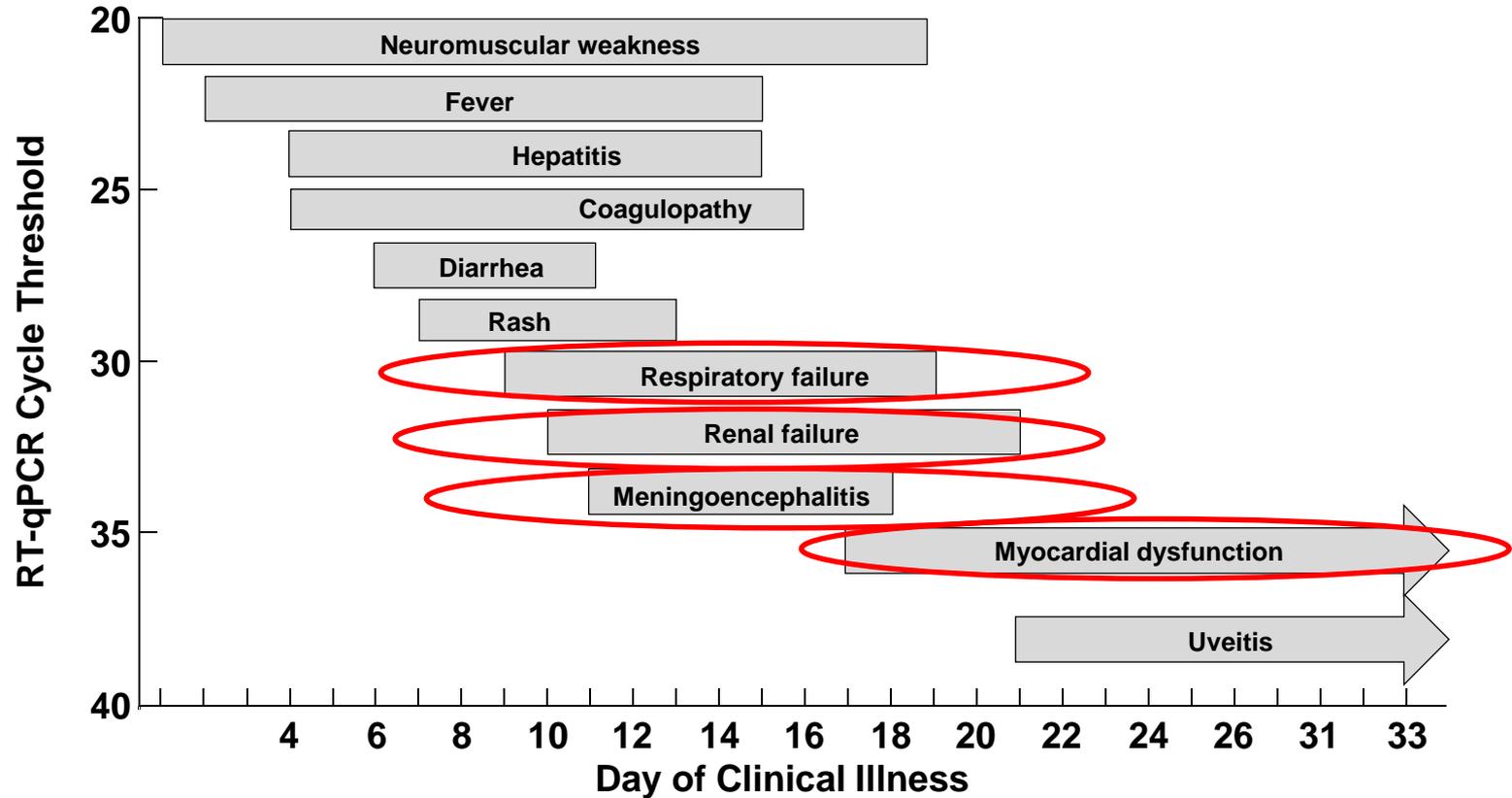
Patient received supportive care alone without experimental therapy



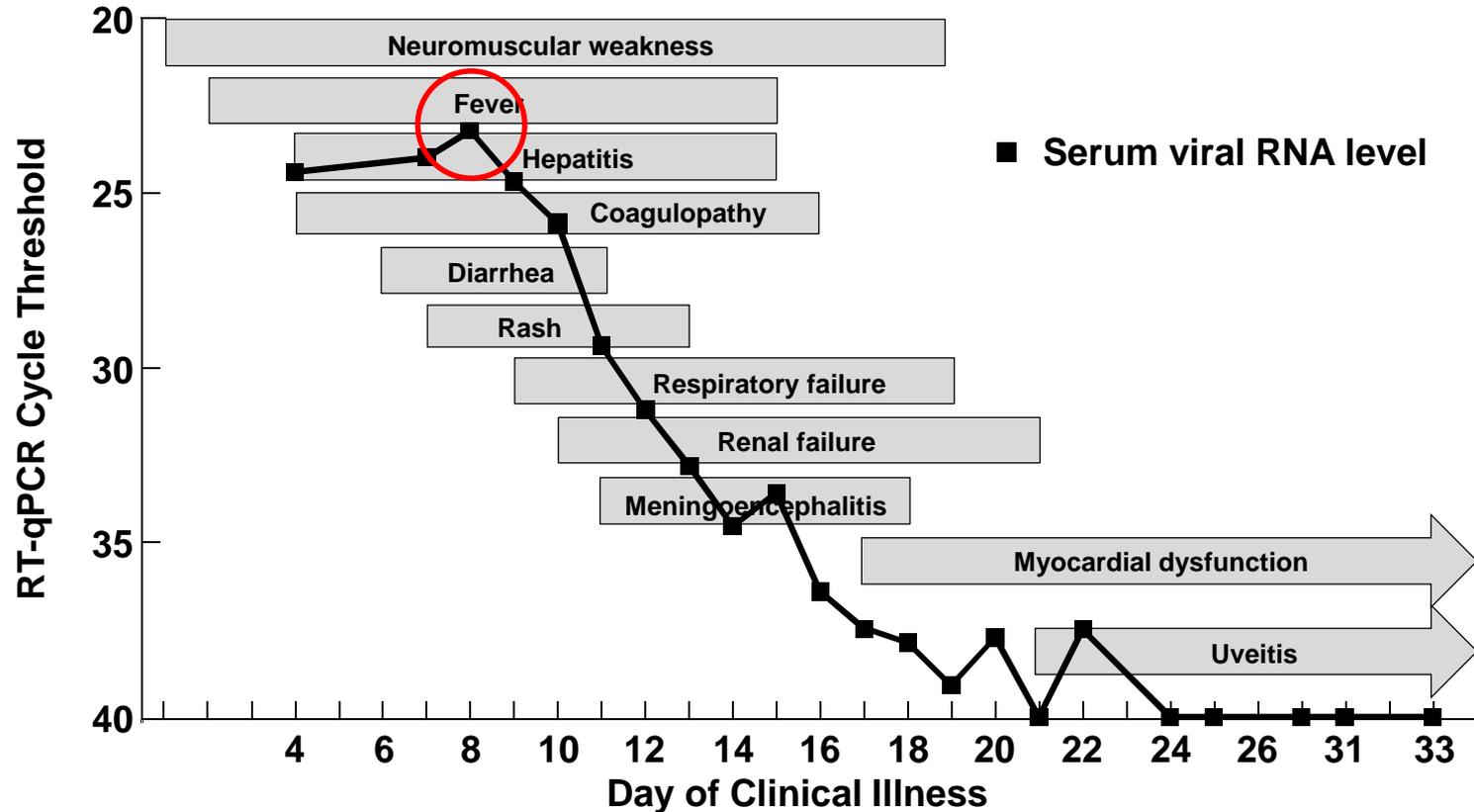
Developed sequential multiorgan failure



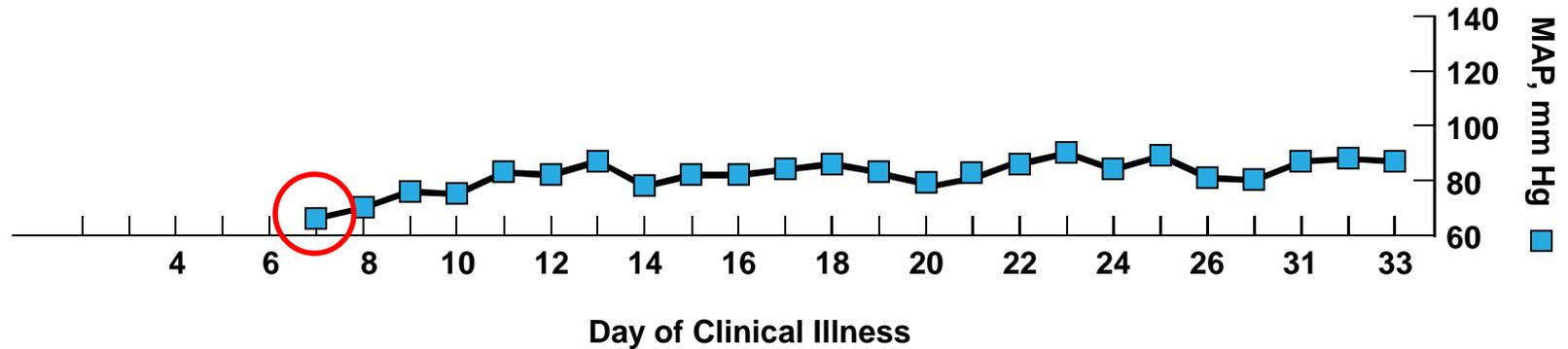
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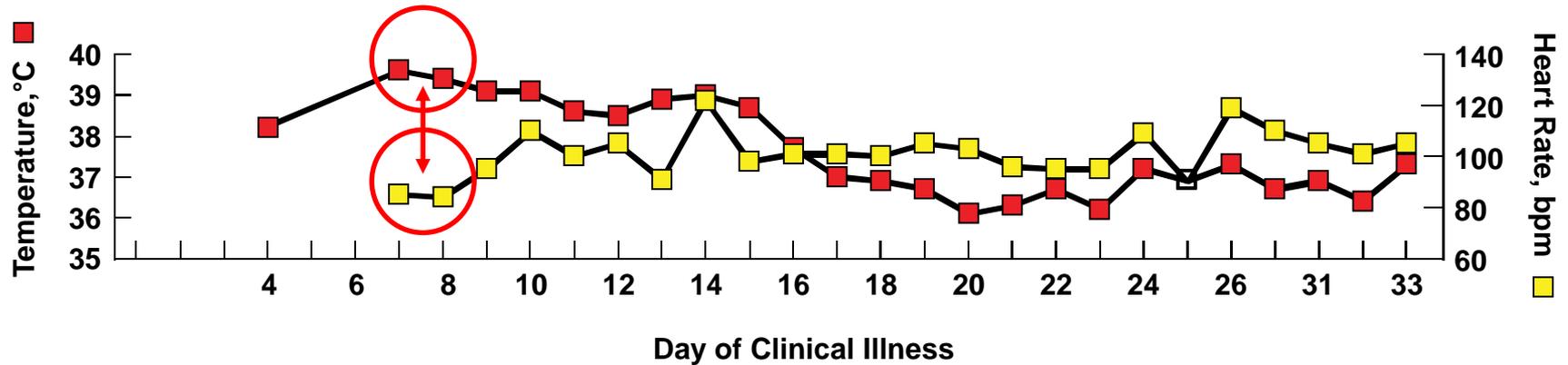
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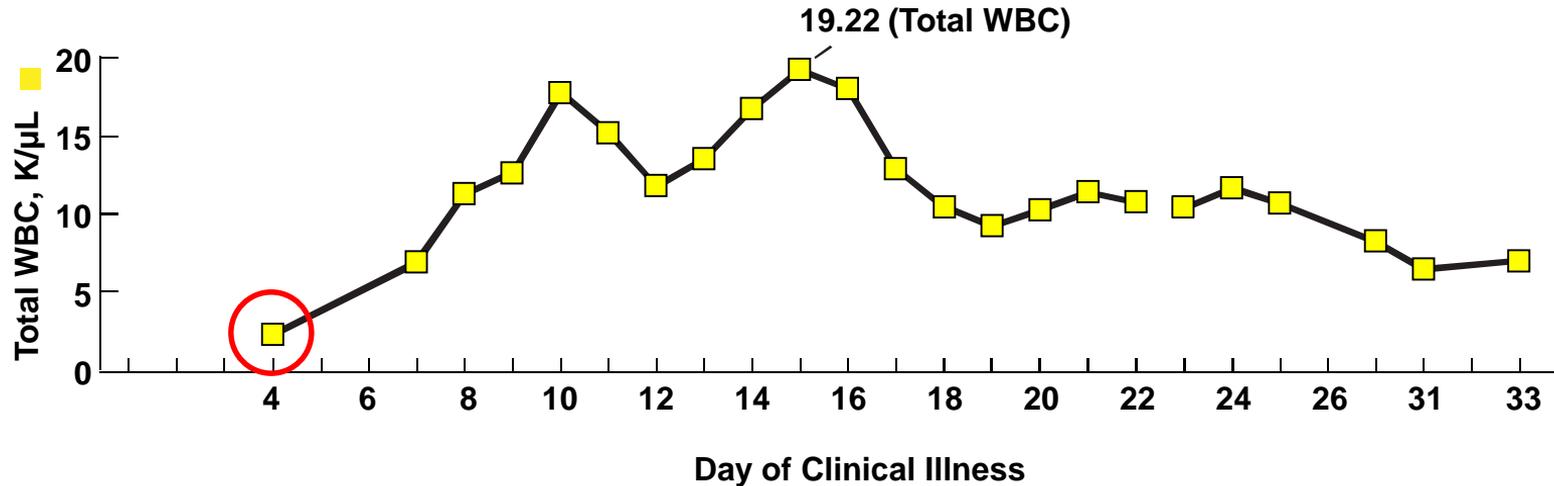
Hemodynamic stability during illness



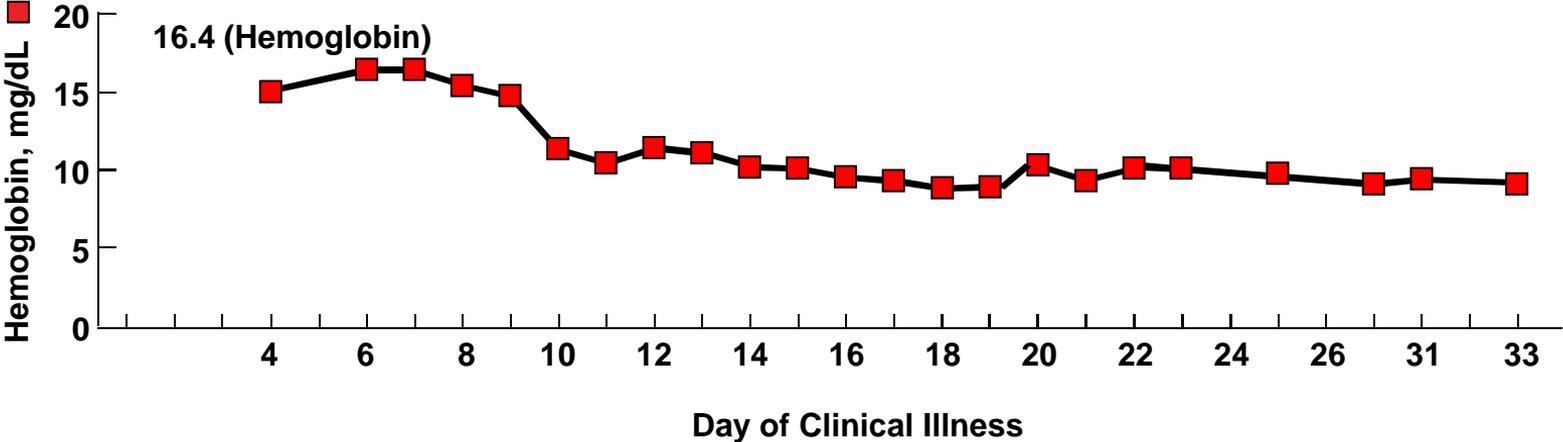
Early temperature-heart rate dissociation



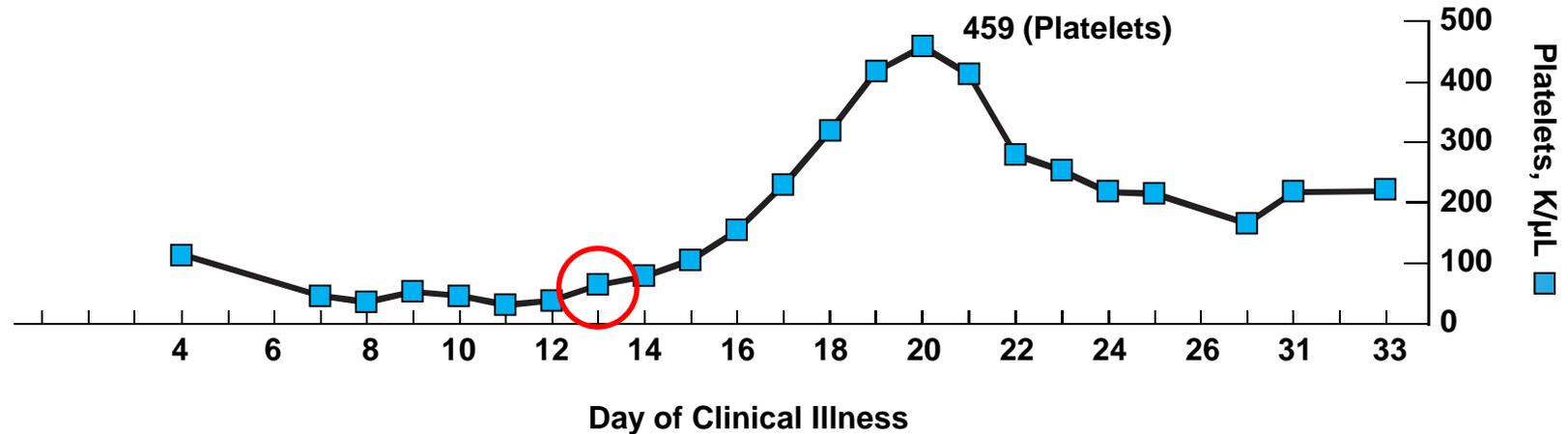
Early leukopenia followed by leukocytosis



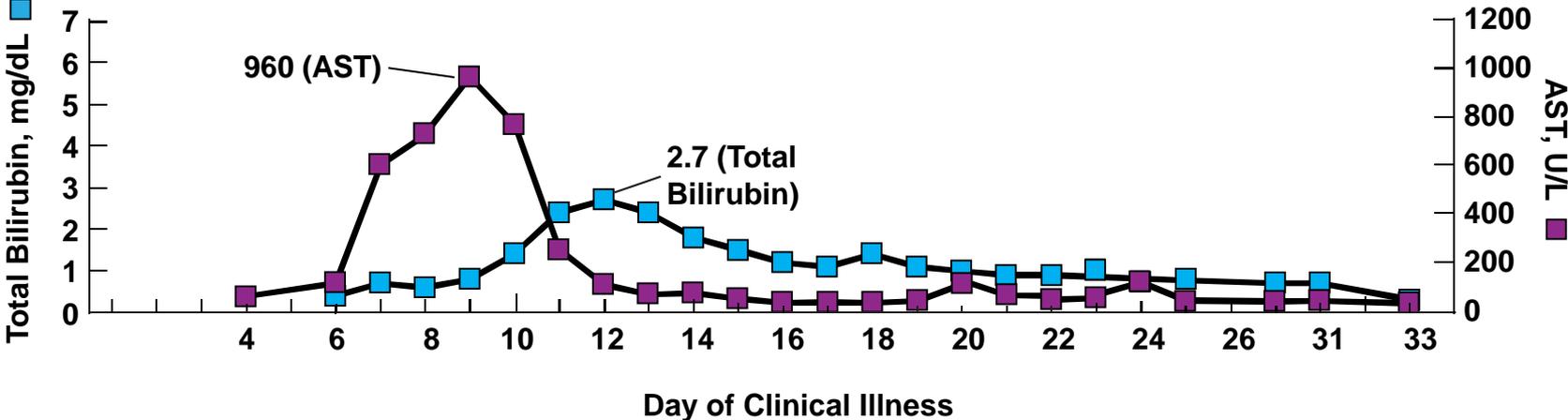
Early hemoconcentration followed by anemia



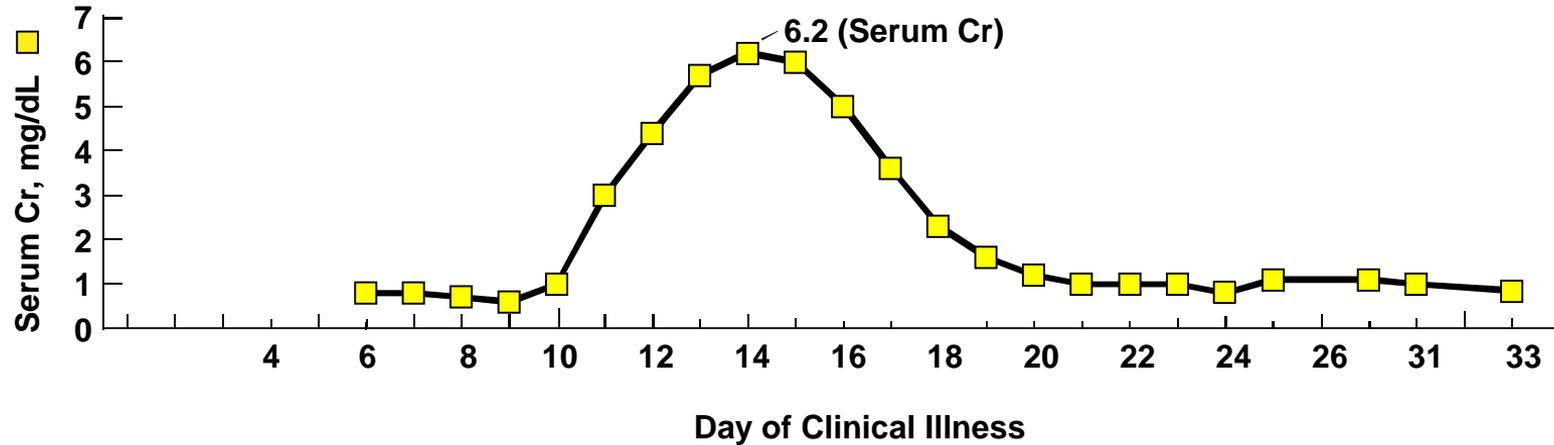
Recovery of platelet count on day 13



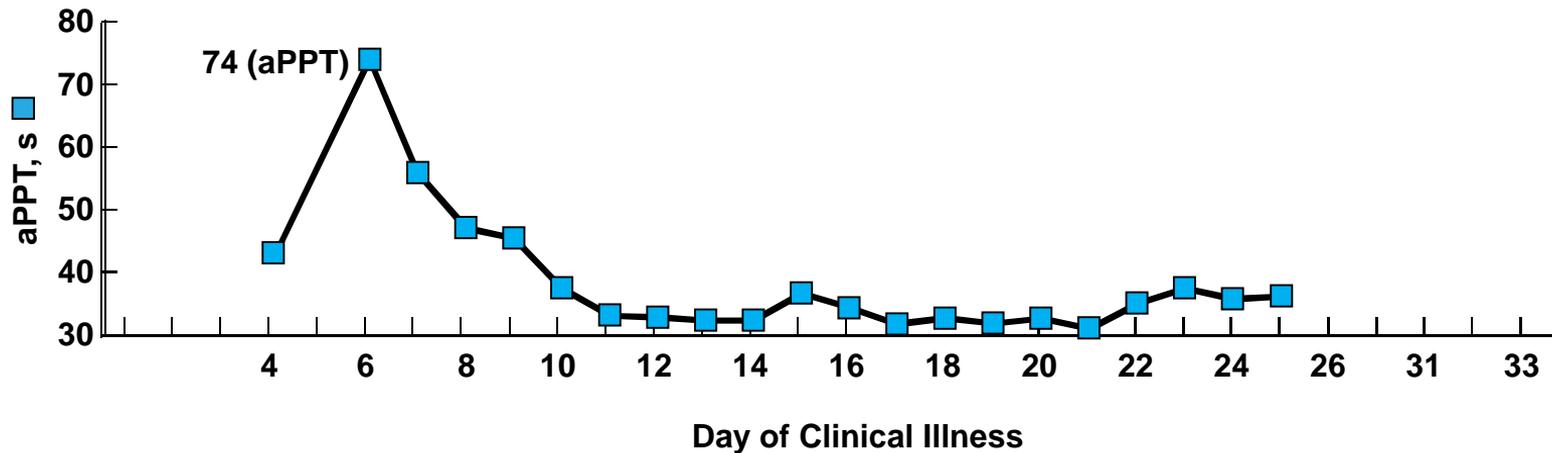
Liver injury peaks at day 9



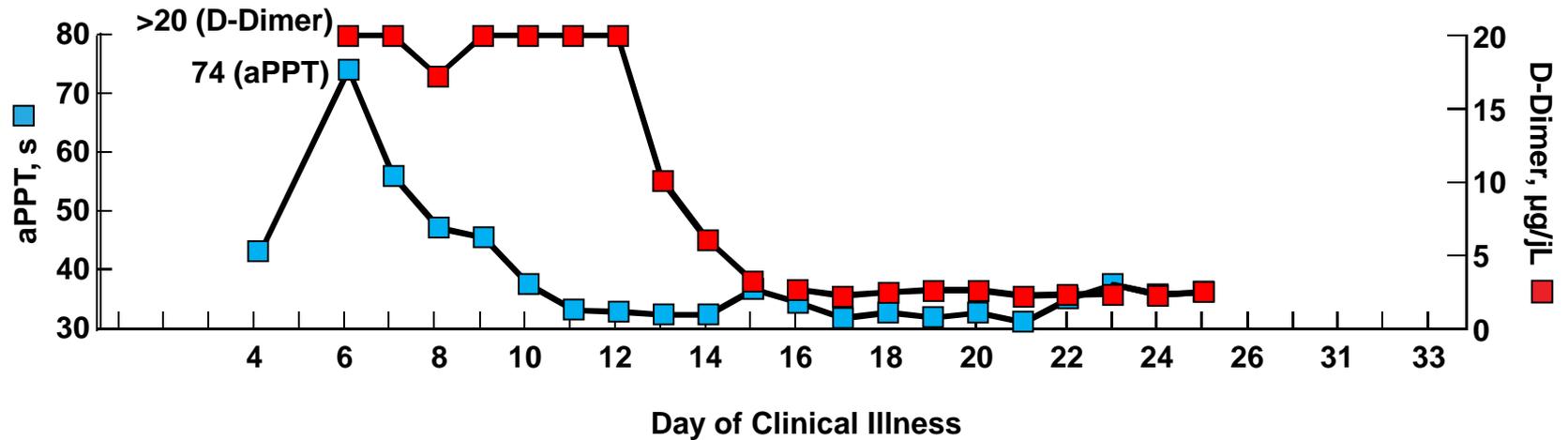
Kidney injury peaks on day 14



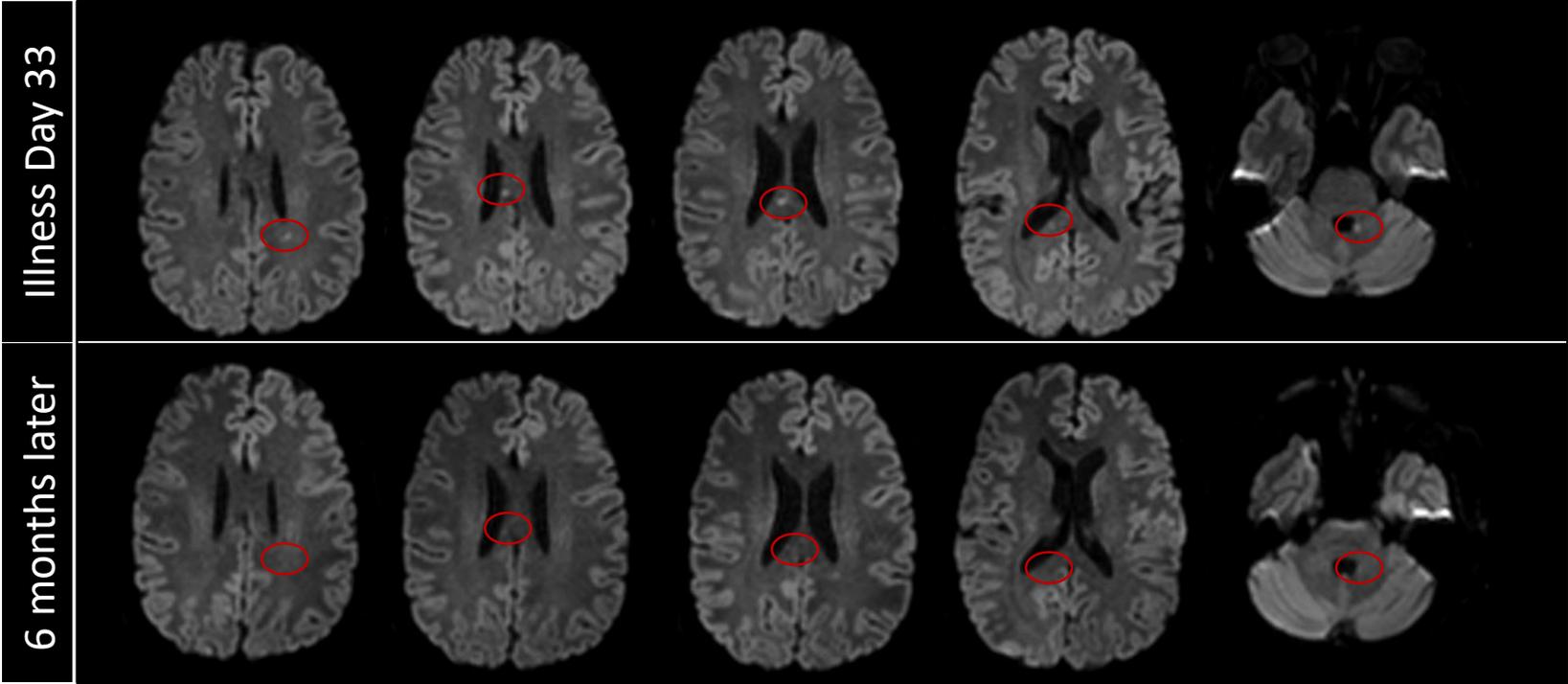
Disseminated intravascular coagulation (DIC) observed early



DIC resolving by day 13

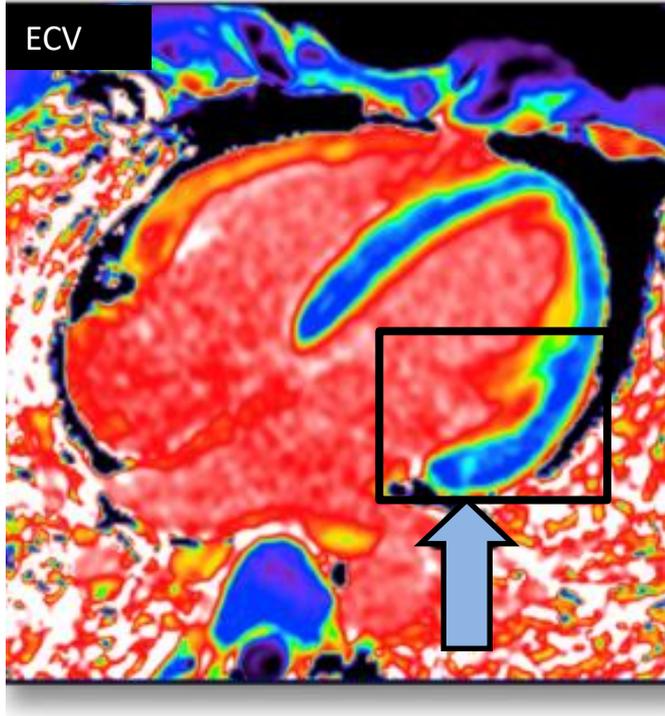


Reversible ischemia detected on brain MRI

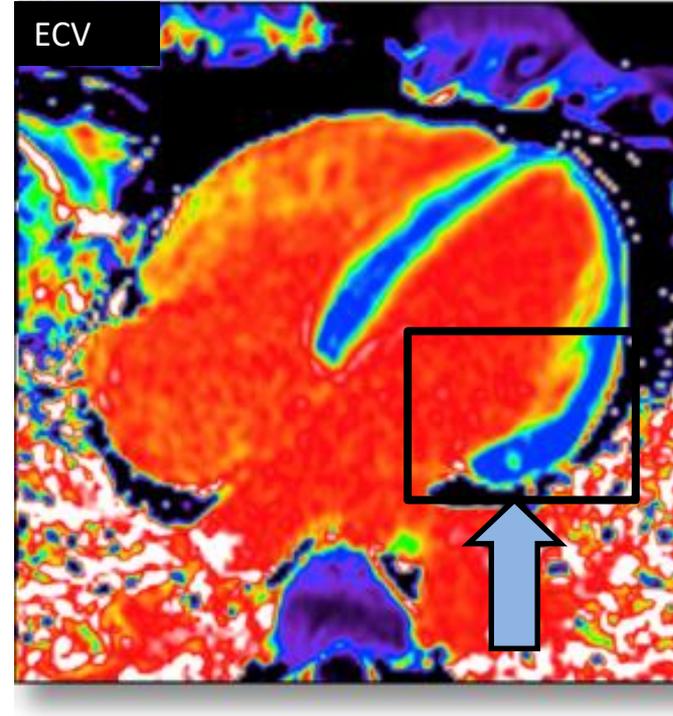


Myocarditis confirmed by cardiac MRI

Illness Day 32

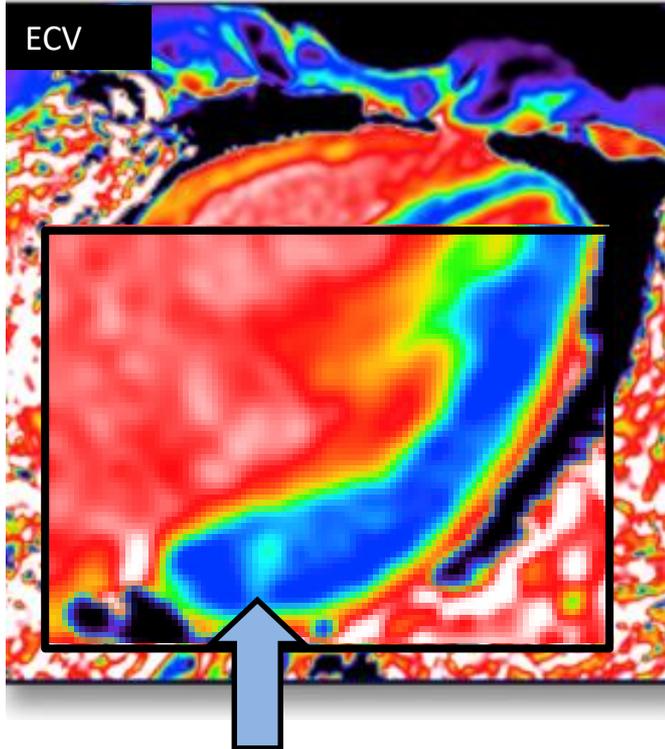


3 months later

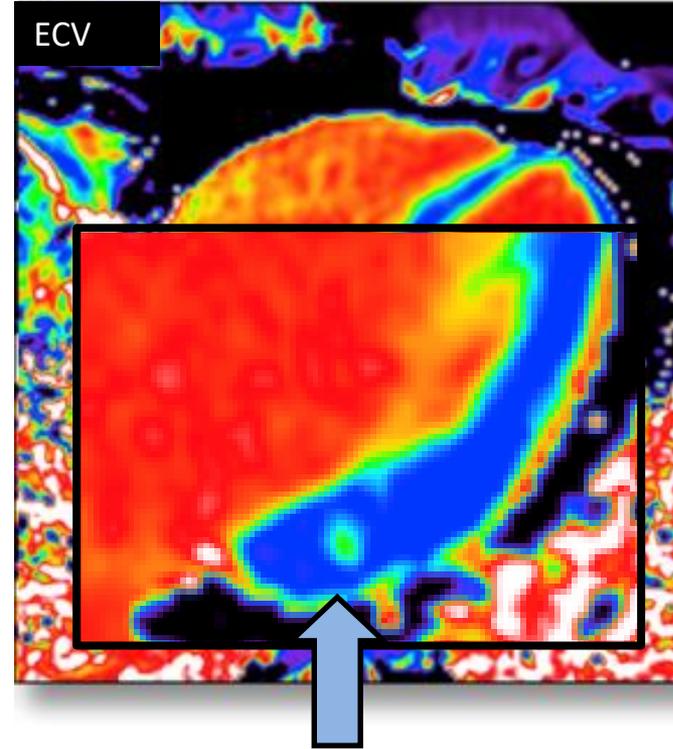


Myocarditis confirmed by cardiac MRI

Illness Day 32

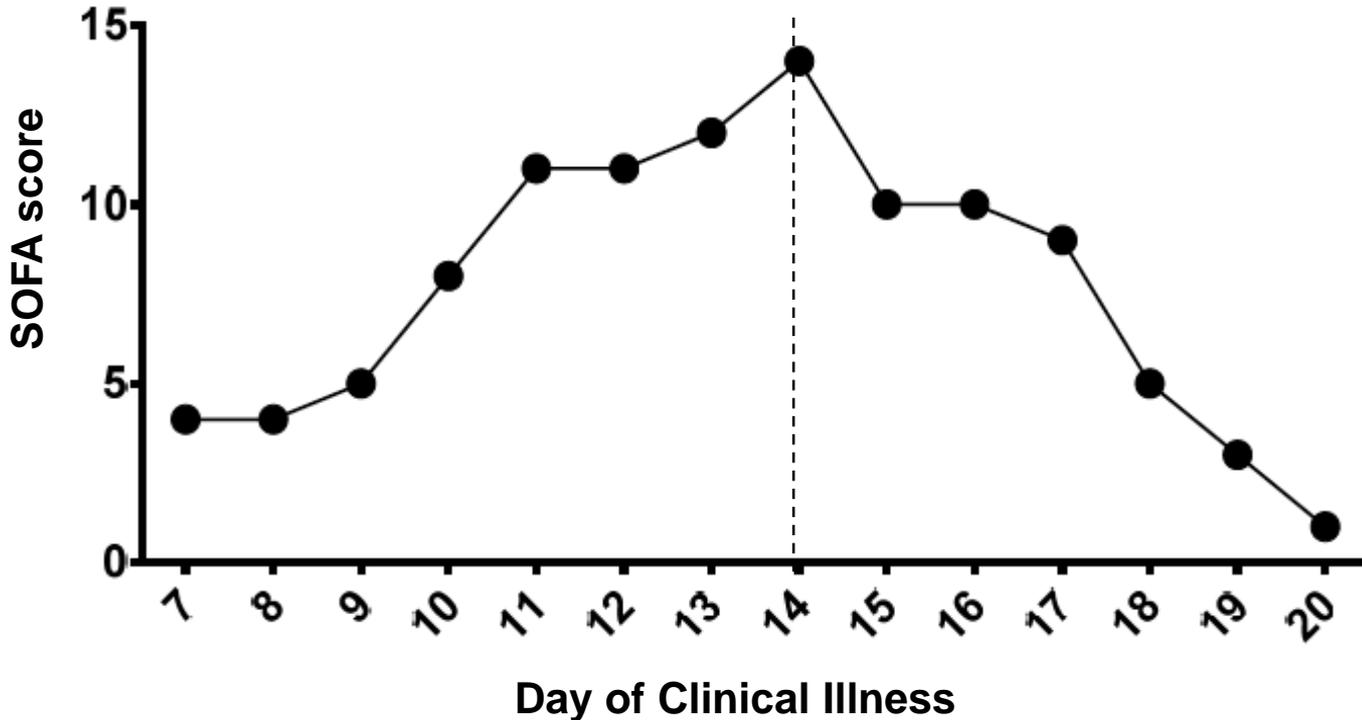


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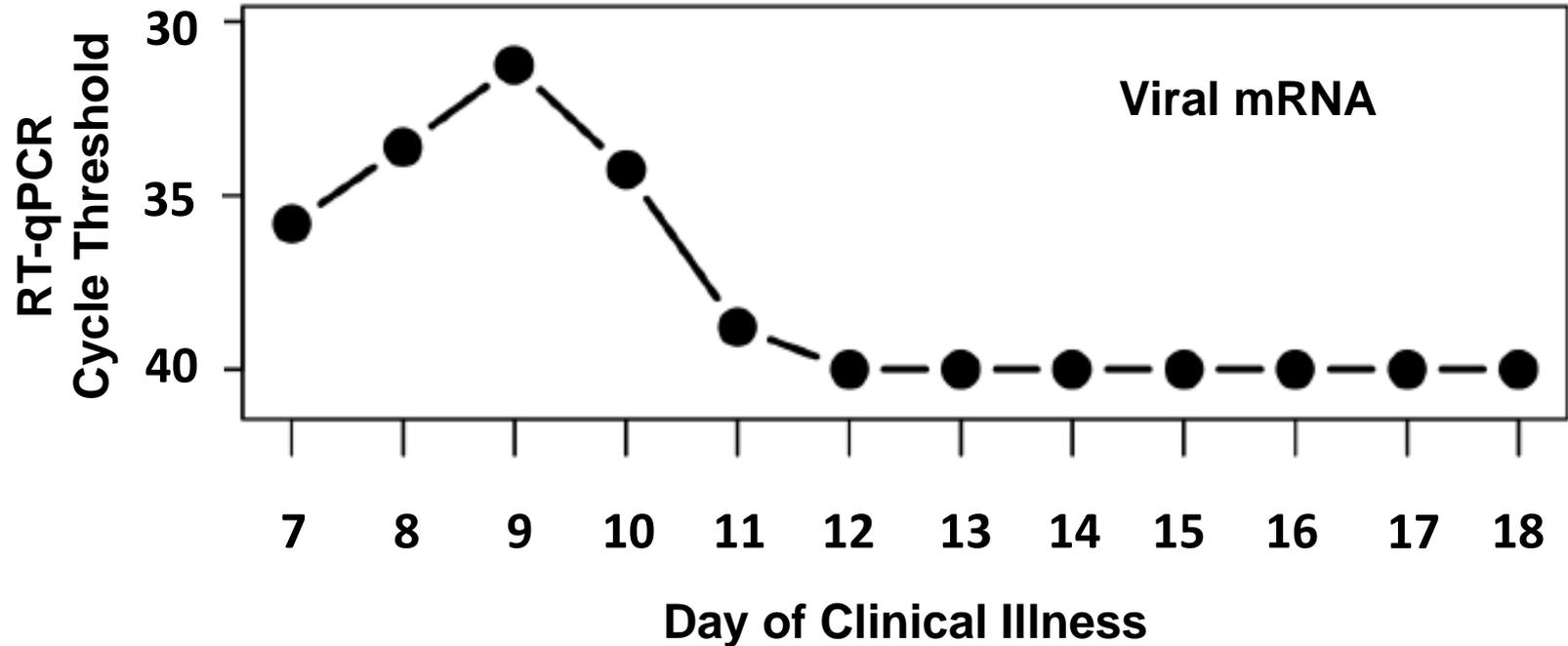


Molecular and immunological correlates of severe EVD in NIH patient

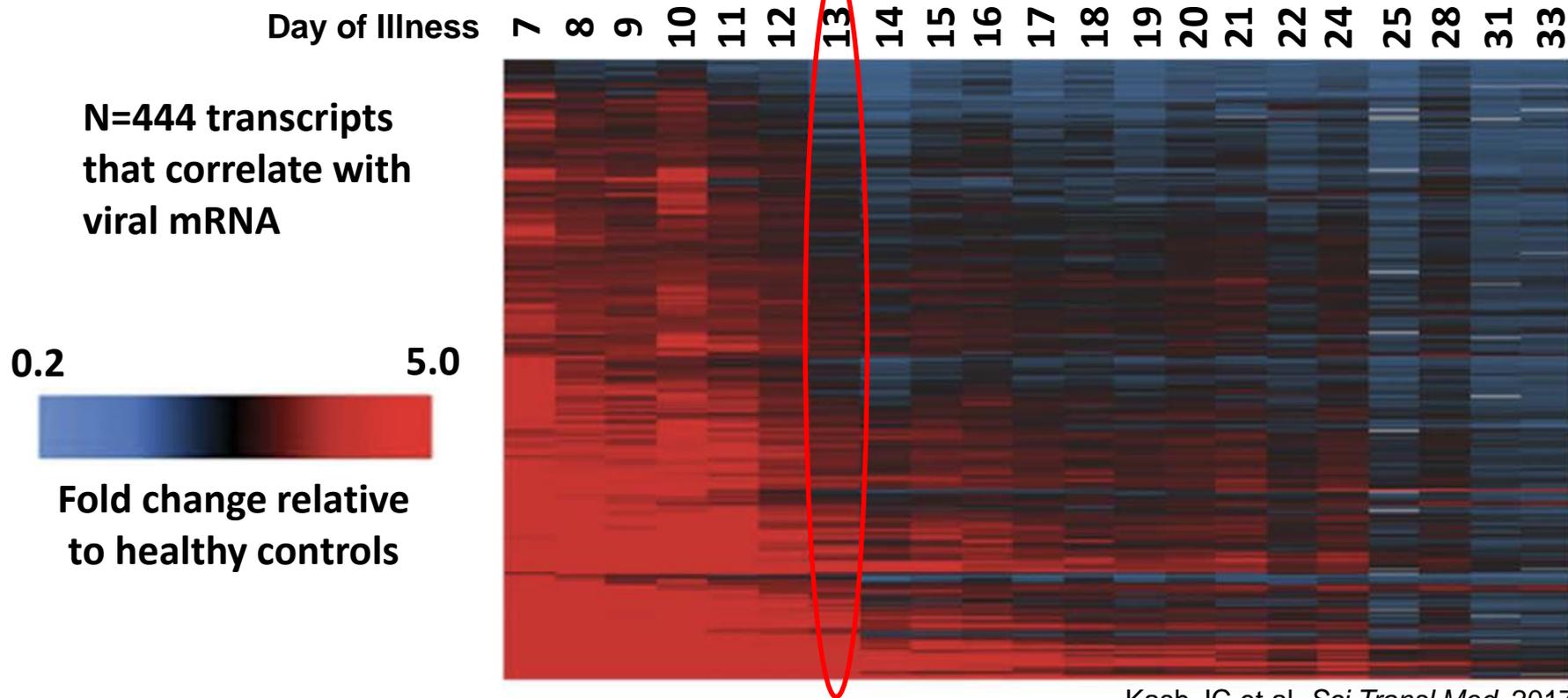
Sequential organ failure assessment (SOFA) score transitions at day 14



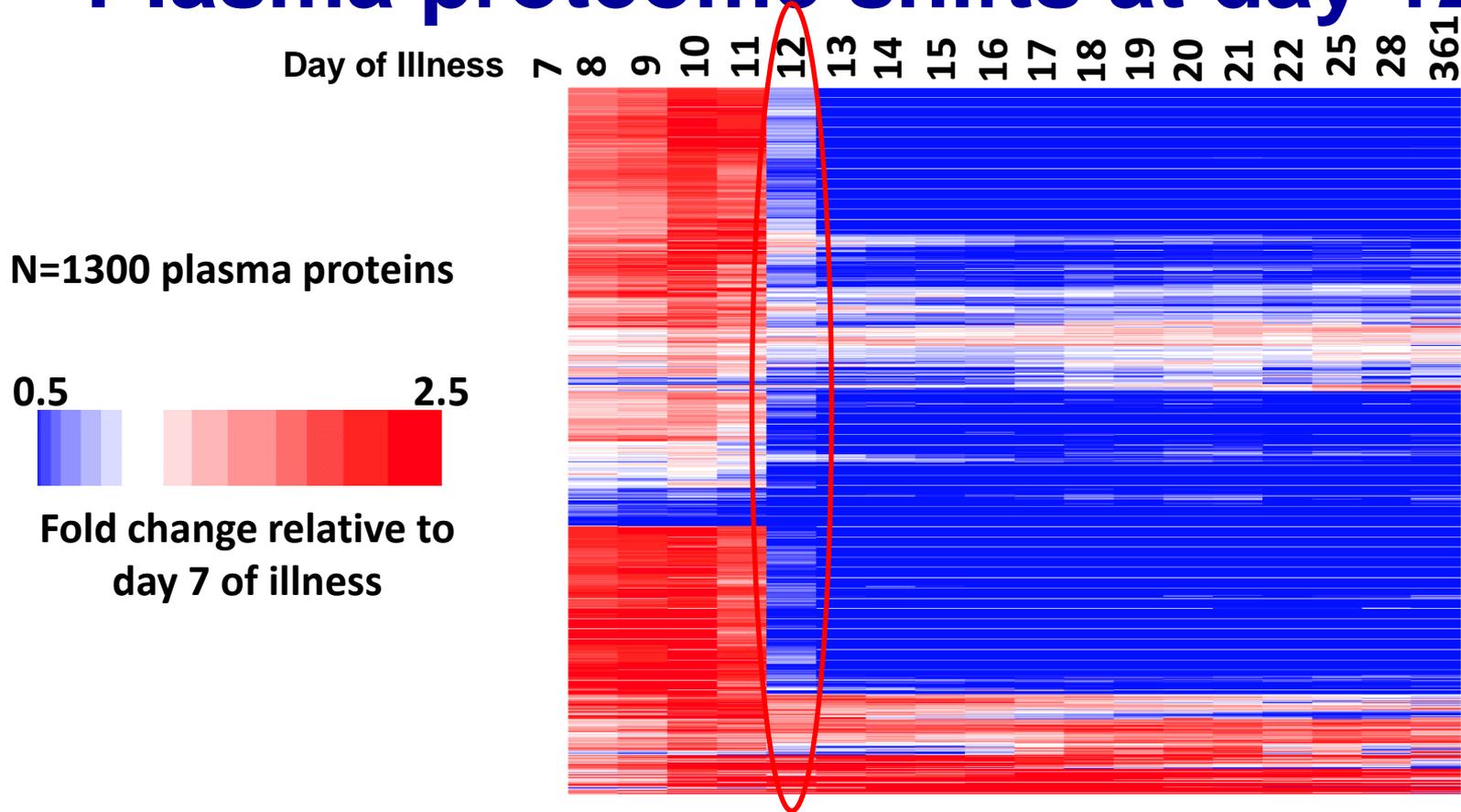
Virus stops replicating in circulating leukocytes by illness day 12



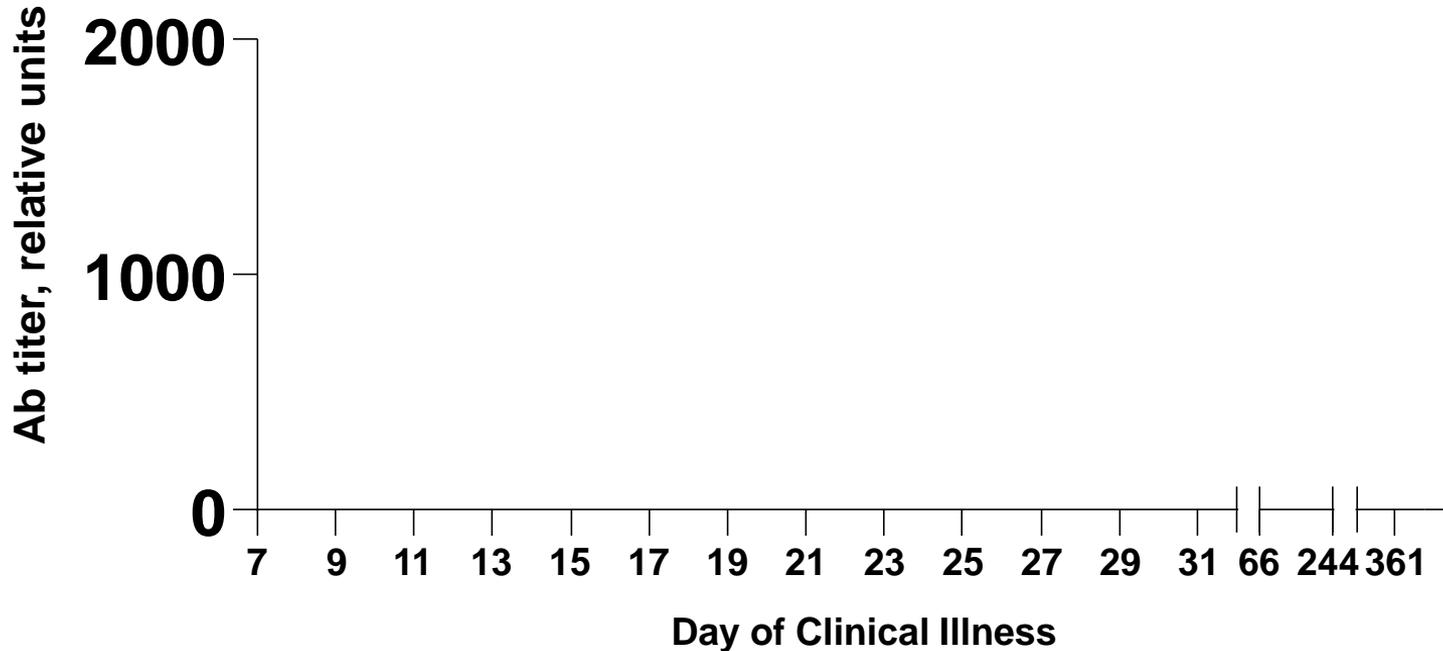
Gene expression profile of circulating leukocytes shifts at day 13



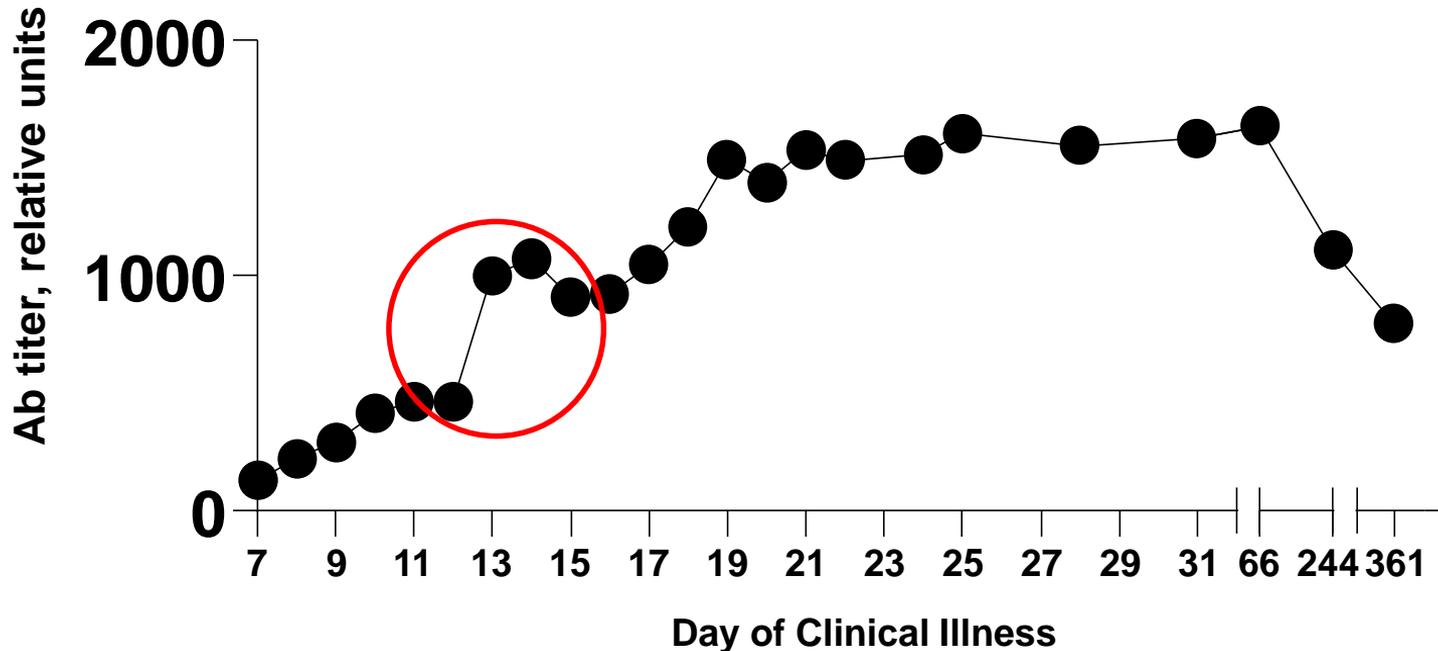
Plasma proteome shifts at day 12



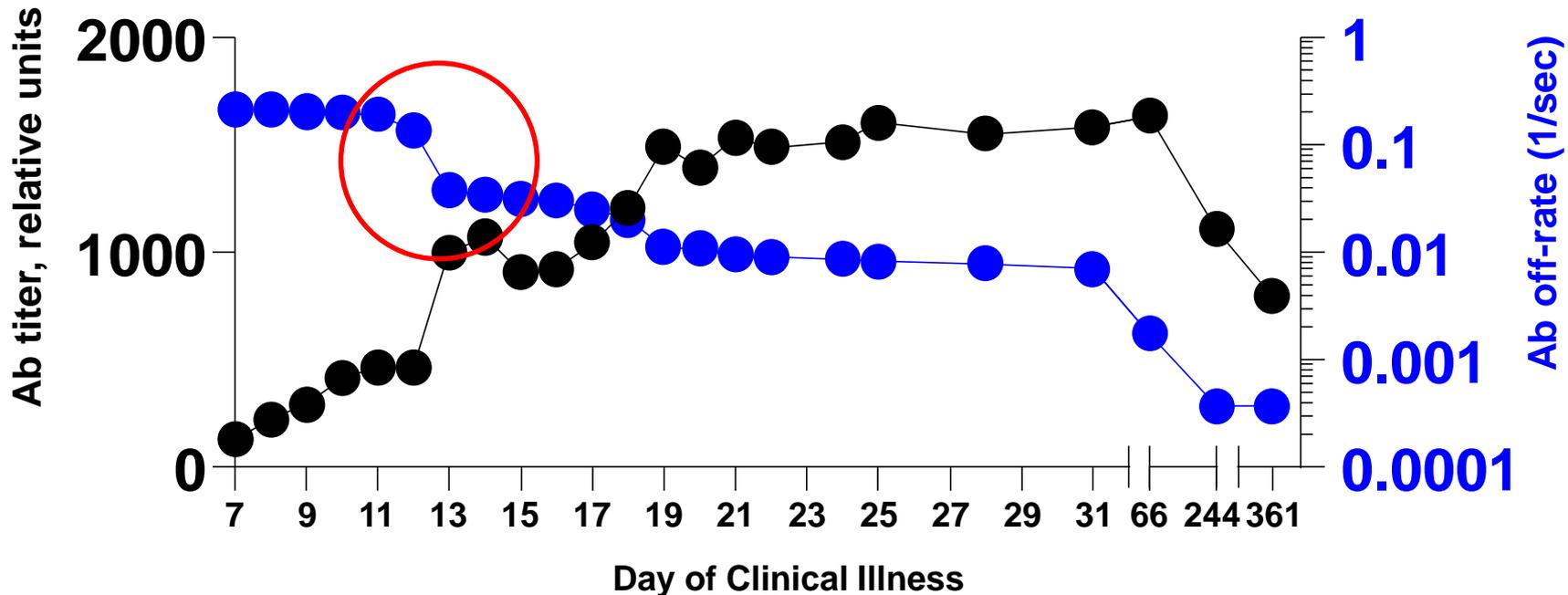
Four-fold rise in Ebola virus (EBOV) glycoprotein (GP) Ab titers on day 13



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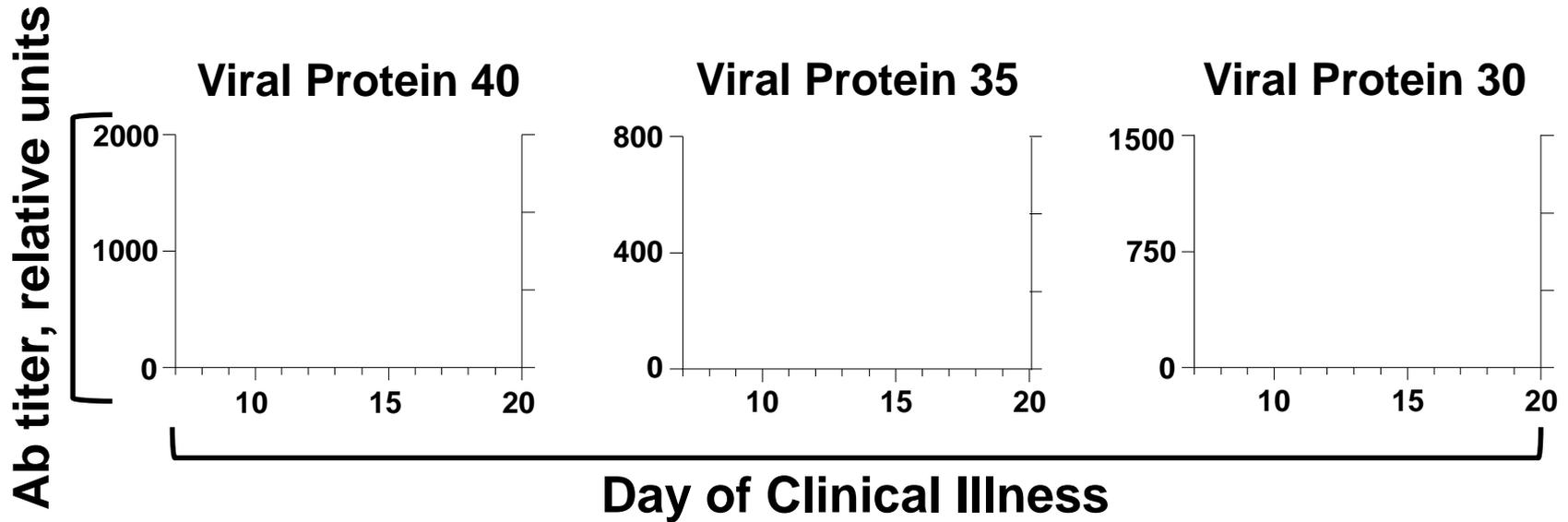
EBOV glycoprotein Ab affinity rises five-fold on day 13



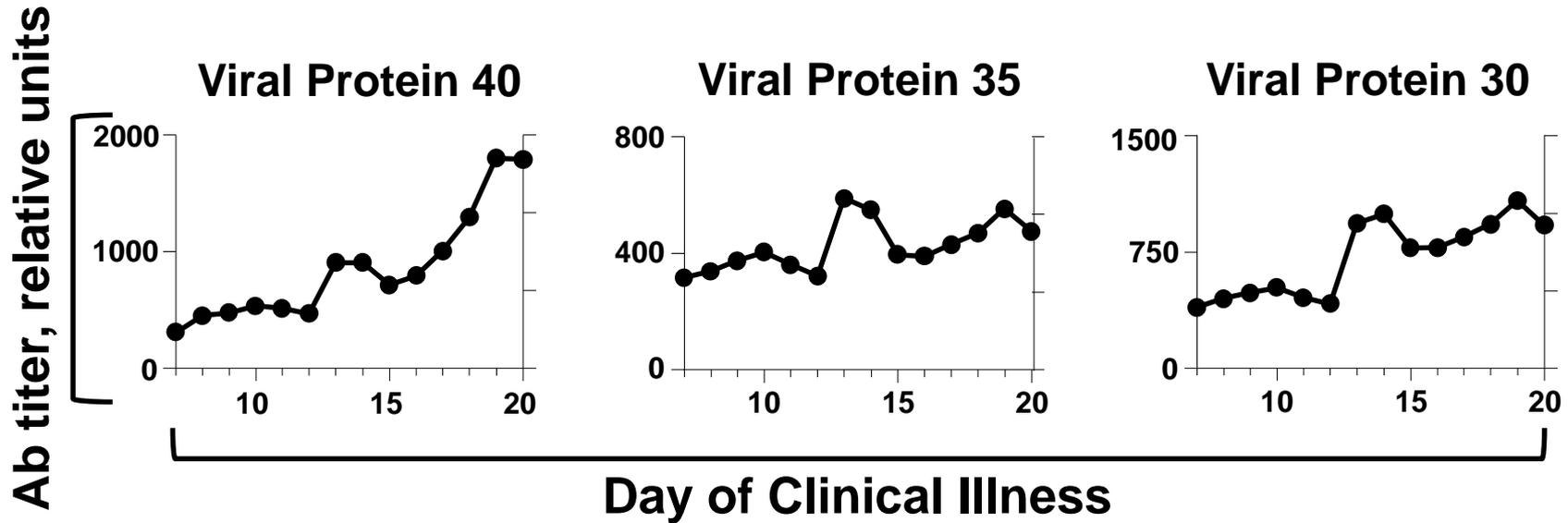
Surface Plasmon Resonance (SPR) assay

Khurana S et al. *Cell Host Microbe*. 2019; in press.

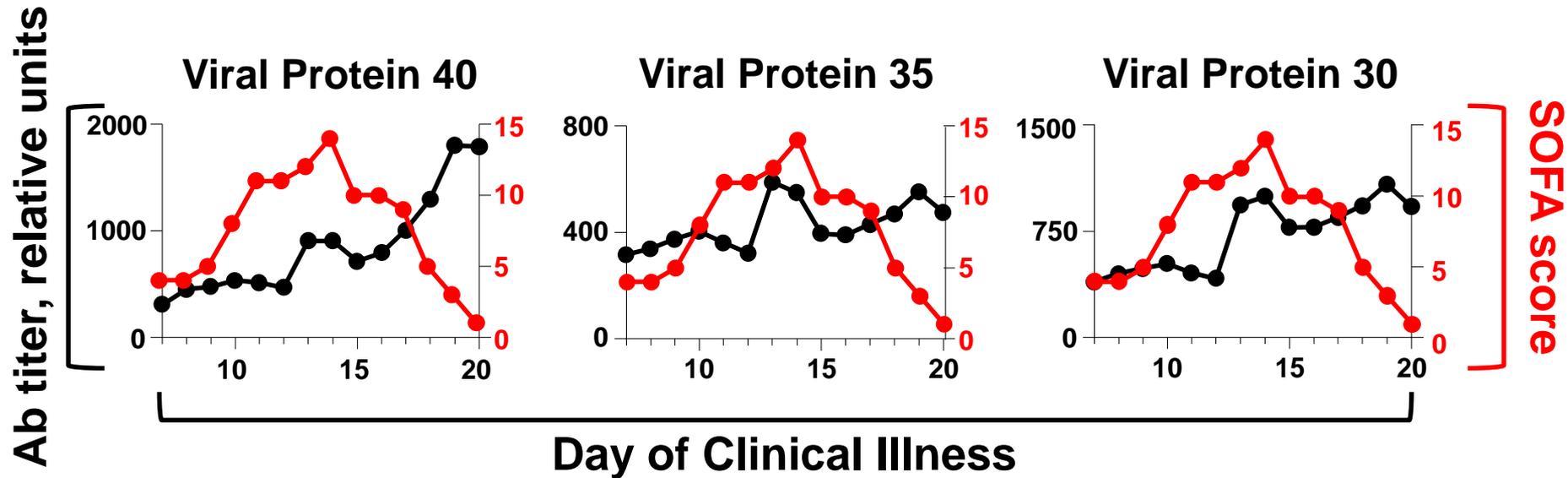
Day 13 rise in Ab titers was observed across all EBOV proteins



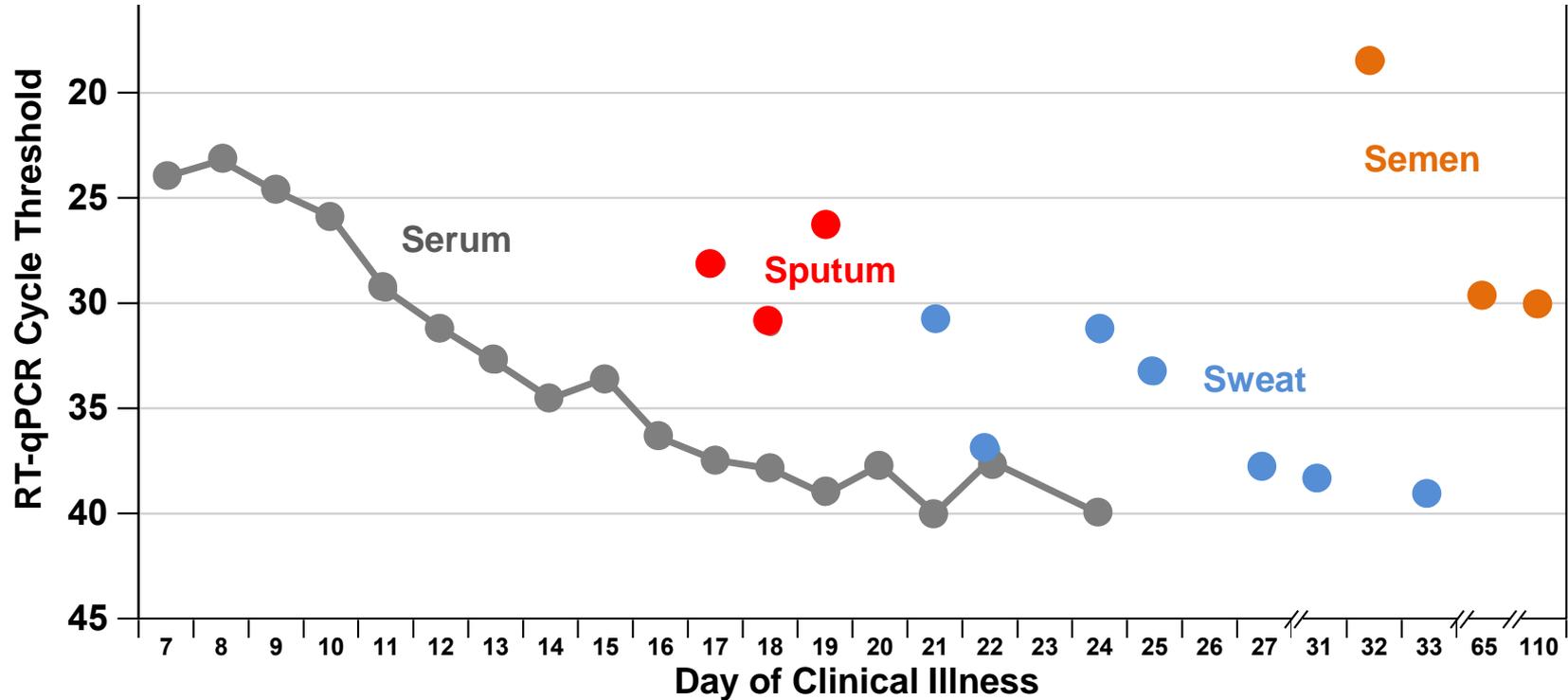
Day 13 rise in Ab titers was observed across all EBOV proteins



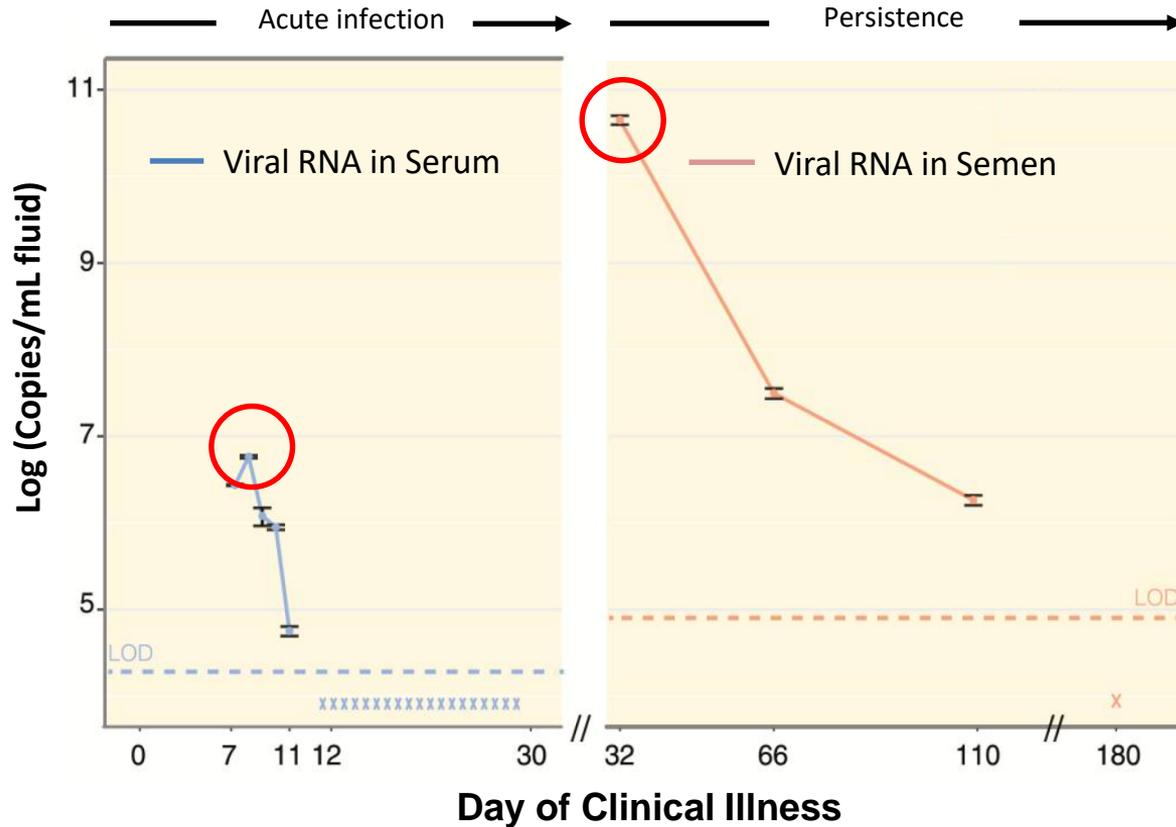
Day 13 rise in Ab titers to all EBOV proteins correlates with decreased SOFA



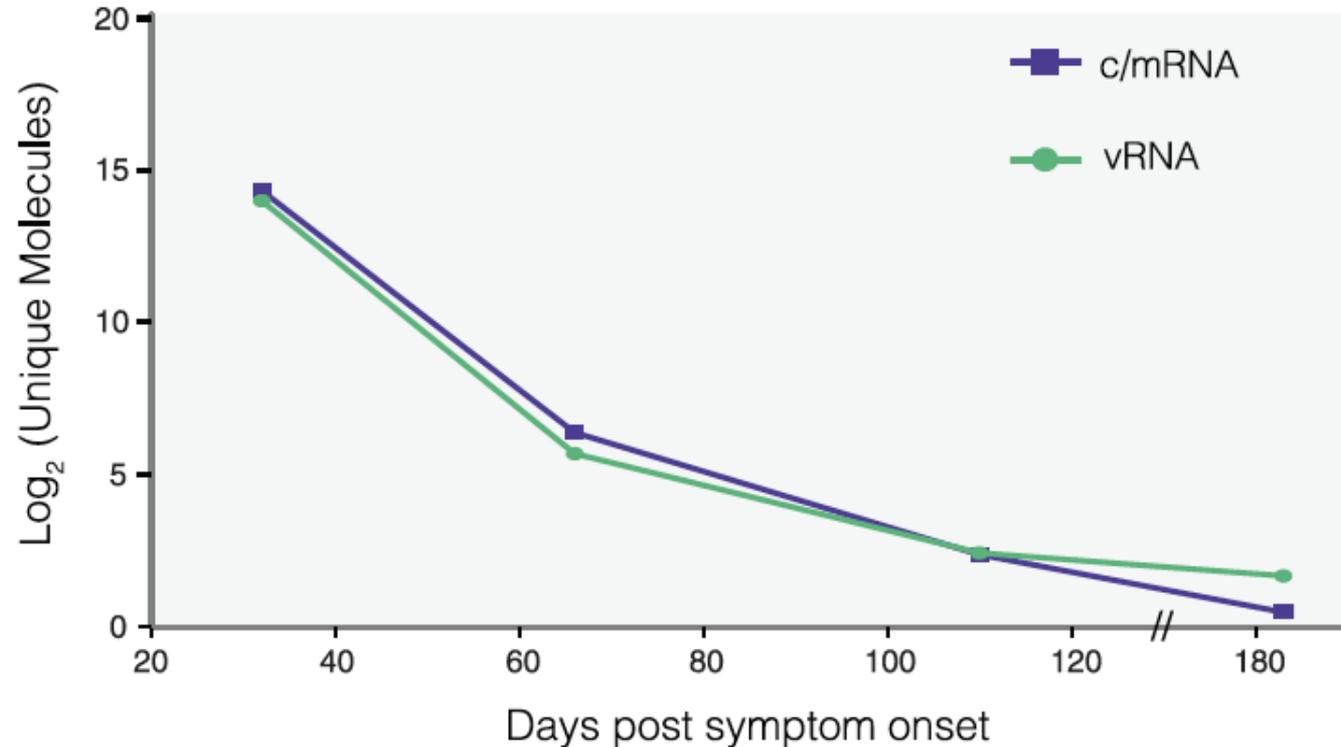
Viral clearance varies across anatomic compartments



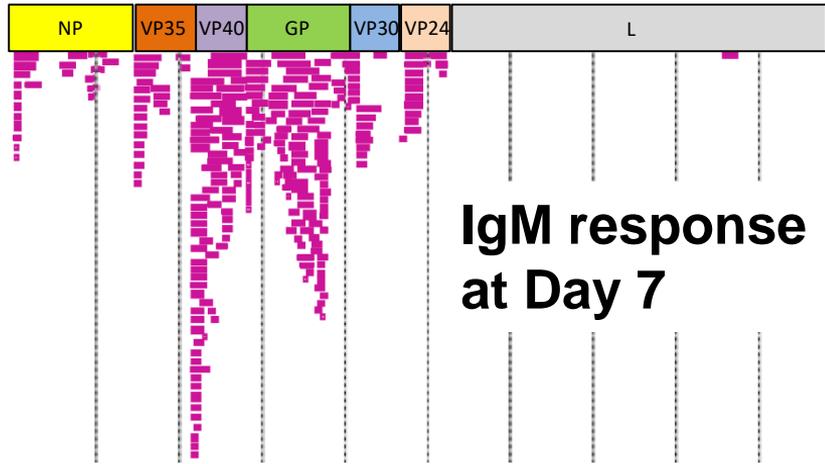
EBOV concentration in semen > serum



Virus replicating in semen at day 110

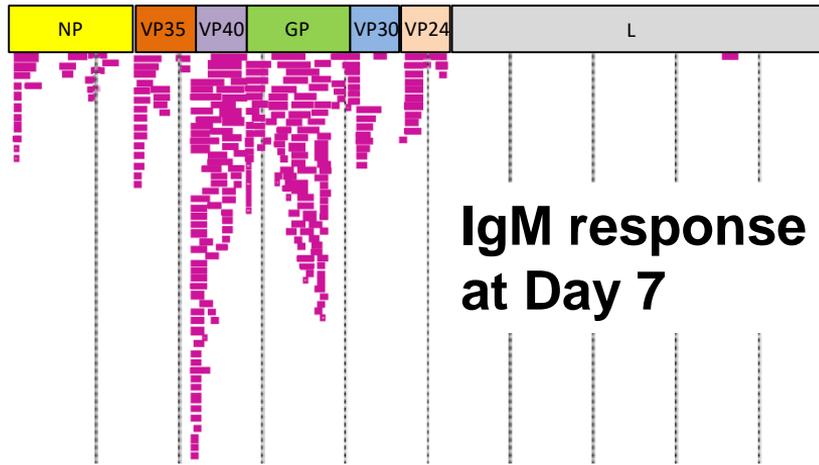


Persistent IgM response across EBOV proteome at day 361

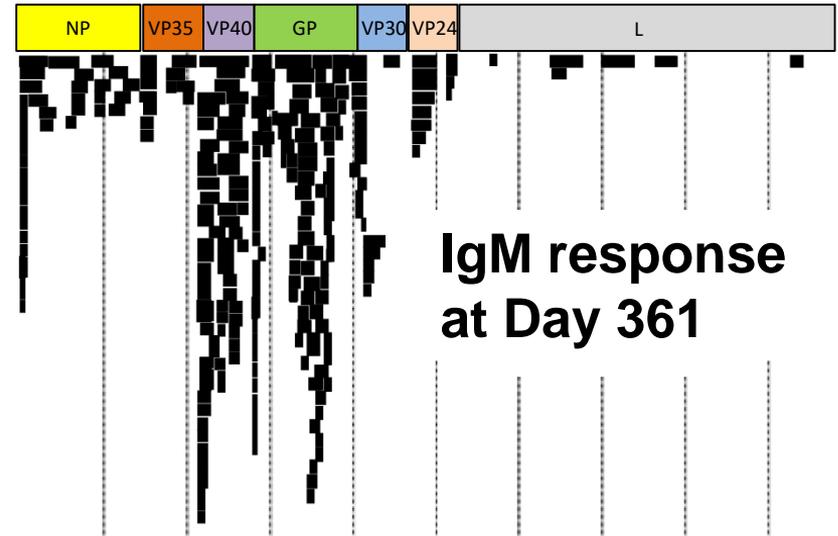


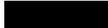
 Viral epitopes detected at day 7 by GFPDL

Persistent IgM response across EBOV proteome at day 361



 Viral epitopes detected at day 7 by GFPDL



 Viral epitopes detected at day 361 by GFPDL

Longitudinal evaluation of EVD survivors and controls

2013–2016 West Africa EVD outbreak



~17,000 survivors

Longitudinal evaluation of EVD survivors and controls

2013–2016 West Africa EVD outbreak



Sierra Leone

Guinea

Liberia

~17,000 survivors

1 year

Enrollment

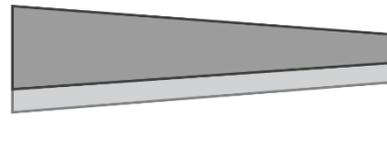
Survivors
($n = 966$)



Controls
($n = 2,350$)



Targeted symptoms



Uveitis



■ Survivors ■ Controls

1-year follow-up

Survivors
($n = 860$)



Persistence of virus in sperm
(30% of men)

Controls
($n = 2,053$)



EBOV RNA commonly persists in semen despite PCR-negative semen testing

- 44% of these men had 2 PCR-negative semen tests followed by a positive test
- Prior studies confirm sexual transmission occurs as late as 1 year after acute illness
- Highlighting the need for an accurate serologic test of EBOV persistence

Future work

- Expand molecular/immunologic inquiries to ELWA-3 cohort (n=1134 samples) to clarify:
 - Relationship between viral replication and host response
 - Immunodominant EBOV epitopes
 - Pathogen/host markers of early and persistent infection
 - Possible targets for host-directed therapies during later stages of EVD